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Residual Kidney Function and Cause-Specific Mortality Among Incident Hemodialysis Patients

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Introduction: The survival benefit of residual kidney function (RKF) in patients on hemodialysis is presumably due to enhanced fluid management and solute clearance. However, data are lacking on the association of renal urea clearance (CL_{urea}) with specific causes of death.

Methods: We conducted a longitudinal cohort study of 39,623 adults initiating thrice-weekly in-center hemodialysis from 2007 to 2011 and had data on renal CL_{urea} and urine volume. Multivariable cause-specific proportional hazards model was used to examine the associations between baseline RKF and cause-specific mortality, including sudden cardiac death (SCD), non-SCD cardiovascular death (CVD), and non-CVD. Restricted cubic splines were fitted for change in RKF over 6 months after initiating hemodialysis.

Results: Among 39,623 patients with data on baseline renal CL_{urea} and urine volume, there was a significant trend toward a higher mortality risk across lower RKF levels, irrespective of cause of death in a case-mix adjustment model ($P_{trend} < 0.05$). Adjustment for ultrafiltration rate (UFR) slightly attenuated the association between low renal CL_{urea} and high cause-specific mortality, whereas adjustment for highest potassium did not have substantial effect. Among 12,169 patients with data on change in RKF, a 6-month decline in renal CL_{urea} showed graded associations with SCD, non-SCD CVD, and non-CVD risk, whereas the graded associations between faster 6-month decline in urine output and higher death risk were clear only for SCD and non-CVD.

Conclusion: Lower RKF and loss of RKF were associated with higher cause-specific mortality among patients initiating thrice-weekly in-center hemodialysis.

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The 5-year mortality rates among patients on dialysis in the United States remains above 50%, which is equal to or worse than that for colorectal cancer or non-Hodgkin's lymphoma.[1,2] Further investigation of the specific factors underlying the cause of death may reveal potential mechanisms responsible for the extraordinary high risk of death among dialysis patients.

RKF is associated with improved survival among patients on hemodialysis.[3–5] RKF substantially contributes to the maintenance of fluid and electrolyte balance and enhanced clearance of both middle molecules and protein-bound solutes.[4,6–8] Therefore, it is postulated that RKF could lead to better cardiovascular outcomes.[5] In exploring the relationship between RKF and CVD, large cohort studies suggested that increased ultrafiltration volumes were associated with high risk of

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SCD.[9,10] The accumulation of potassium over the long interdialytic interval is known to cause hyperkalemia, which could result in cardiac arrhythmias and SCD.[11,12]

On the other hand, a previous study based on a large European registry suggested that excess mortality among patients starting dialysis was not specifically due to increased cardiovascular mortality but also due to similarly elevated noncardiovascular mortality.[13] Furthermore, in a community-based cohort study, noncardiovascular mortality increased with lower kidney function in elderly patients with chronic kidney disease.[14] Several basic studies have demonstrated that retention of uremic toxins contributes to the susceptibility to infection, the leading cause of non-CVD among patients on dialysis.[15-18] Given that RKF provides continuous clearance of middle molecules and protein-bound solutes,[7,19,20] the benefits of RKF may extend to noncardiovascular morbidity and mortality. Indeed, a previous study showed that greater RKF was associated with a lower risk of non-CVD among patients on peritoneal dialysis.[21] However, few studies have investigated such relationship in patients on hemodialysis.

Additional studies examining the relationship between RKF and cause-specific mortality in patients on hemodialysis are needed to understand the mechanisms underlying their exceptionally high mortality risk and to recognize areas requiring targeted interventions. We therefore conducted a nationally representative cohort study using data from a large dialysis organization in the United States to examine the association of RKF with SCD, non-SCD CVD, and non-CVD among patients initiating thrice-weekly in-center hemodialysis.

METHODS

Study Design and Population

We analyzed longitudinal data from a retrospective cohort study of incident dialysis patients aged 18 years or older who received treatment for at least 60 days at a facility operated by a large dialysis organization in the United States from January 1, 2007 to December 31, 2011. The follow-up period was divided into patient-quarters (i.e., successive 91-day periods from date of first dialysis). Patients who did not receive thrice-weekly in-center hemodialysis for at least 45 days within each patient-quarter were excluded, as were patients with prior kidney transplantation, resulting in a total cohort of 121,712 patients (Figure 1). Patients with CL_{urea} >15 ml/min per 1.73 m^2 or urine volume >3000 ml/d at the first and/or third patient-quarter were excluded from all analyses. We then identified 39,623 incident in-center hemodialysis patients who had data on residual renal CL_{urea} during the first patient-quarter, which was defined as the baseline quarter. Among them, 12,169 patients (30.6%) who had renal CL_{urea} measurement of both the first and third patient-quarters were used to evaluate the association of change in renal CL_{urea} with cause-specific mortality. This study was approved by the Institutional Review Committee of the University of California

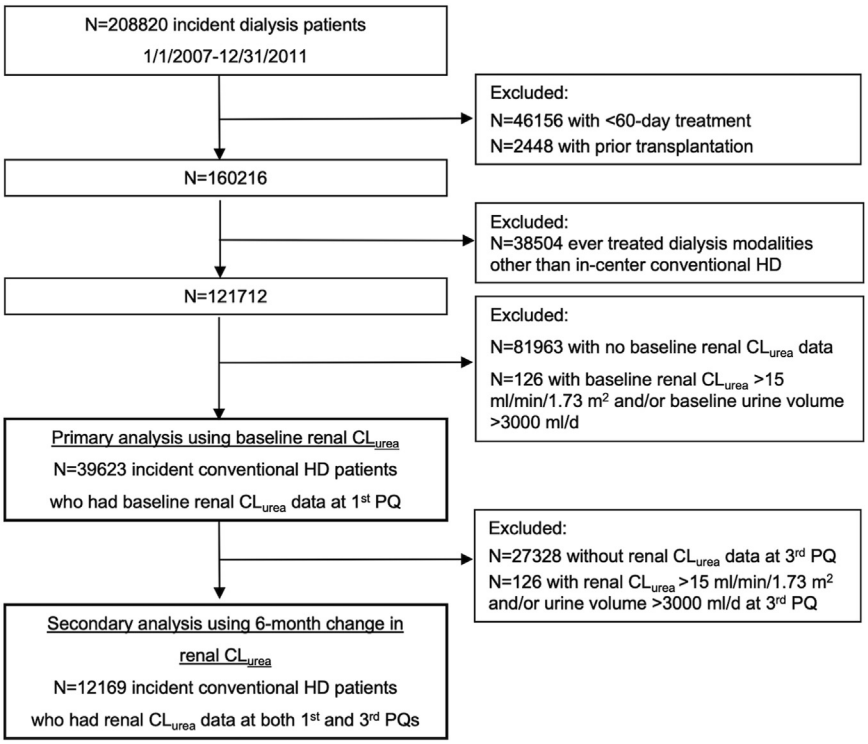

Figure 1. Flow diagram of cohort construction. CL_{urea}, urea clearance; HD, hemodialysis; PQ, patient-quarter.

Irvine Medical Center with exemption from informed consent.

Measurement of RKF

The methodology for the measurement of renal CL_{urea} was based on our prior report with the approach by Daugirdas, which is designed to estimate plasma water urea clearance and not plasma urea clearance.[22,23] The estimating equation is expressed as follows:

$$\text{renal } CL_{urea}\ (\text{ml}/\text{min}) = \frac{\text{urinary urea nitrogen (mg/dl)} \times \text{urinary volume (ml)}}{\text{collected time (min)} \times [0.9 \times \text{serum urea nitrogen (mg/dl)}]}$$

Among all the eligible renal CL_{urea} observations, the percentage of urine collection time reported as 1440 minutes was 98.1%, ranging from 720 to 2880 minutes. Renal CL_{urea} was adjusted for body surface area according to the prior literature.[23,24]

Outcomes

Outcomes were cause-specific mortality, including the following: (i) SCD, (ii) non-SCD CVD, and (iii) non-CVD. Data on each cause of death were obtained from the provided database that used the same categories of the Centers for Medicare and Medicaid Services form 2746, including a list of 70 possible entries for cause of death.[1] Consistent with the established cause-of-death classification system used for decades in the United States Renal Data System,[12,25,26] SCD was defined as death due to "Cardiac arrest, cause unknown" and "Cardiac arrhythmia" on form 2746 as shown in Supplementary Table S1.[1] Non-SCD CVD was defined as death attributable to acute myocardial infarction, atherosclerotic heart disease, congestive heart failure, cerebrovascular accident, and other cardiovascular causes excluding SCD. Non-CVD was death from infectious diseases, malignancy, withdrawal from dialysis or uremia, and all other known causes (Supplementary Table S1). Patients were followed-up with until death, 1000 days after initiating maintenance hemodialysis, kidney transplantation, transfer to a facility operated by another dialysis provider, discontinuation of dialysis, and administrative end of follow-up (December 31, 2011).

DATA COLLECTION

All information were obtained from the electronic medical records of the dialysis provider. All laboratory values were measured using standardized automated methods in a central laboratory (Deland, Florida) within 24 hours of blood collection. Laboratory measurements and dialysis treatment parameters were averaged during each 91-day period of the patient-quarter. The highest potassium value recorded during each 91-day period was also extracted and categorized. Normalized protein catabolic rate was calculated accounting for each patient's renal CL_{urea}[27,28] (Supplementary Method S1). The first 91-day period of hemodialysis served as the baseline quarter.

Statistical Analyses

Baseline characteristics were summarized for the entire analytic cohort (N = 39,623) and categorized into 5 groups according to baseline renal CL_{urea} (<1.5, 1.5 to <3.0, 3.0 to <4.5, 4.5 to <6.0, and ≥6.0 ml/min per 1.73 m^2). Trends across baseline renal CL_{urea} categories were assessed using nonparametric trend tests. Crude rates for main outcomes were calculated by examining the percentage of each cause of death in each patient-quarter.

For the primary analysis, associations between baseline renal CL_{urea} categories and cause-specific mortality were analyzed using cause-specific proportional hazards models. Competing risk regression models (Fine and Gray model[29]) were also used for sensitivity analyses. Competing events were defined as deaths due to causes other than the cause of interest. Proportional hazards assumptions were tested by plotting Schoenfeld residuals and log-log survival curves. Adjusted hazard ratios were estimated by analyzing baseline renal CL_{urea} categories as a categorical variable using renal CL_{urea} >6.0 ml/min per 1.73 m^2 as a reference group. Models were examined with 6 levels of sequential adjustments as follows: (i) "unadjusted" model; (ii) "case-mix" adjusted model that included age, sex, race/ethnicity, primary insurance, comorbid conditions (hypertension, diabetes, congestive heart failure, atherosclerotic heart disease, other cardiovascular disease), vascular access type, and single-pool Kt/V; (iii) "case-mix plus highest potassium categories" adjusted model including the case-mix model and 5 categories of highest predialysis serum potassium levels (<5.0, 5.0 to <5.5, 5.5 to <6.0, 6.0 to <6.5, and ≥6.5 mEq/l); (iv) "case-mix plus UFR" adjusted model including case-mix model and UFR; (v) "case-mix plus laboratory" adjusted model including the case-mix model plus body mass index, normalized

protein catabolic rate, hemoglobin, serum albumin, creatinine, highest potassium categories, phosphorus, iron saturation, bicarbonate, and log-transformed alkaline phosphatase and ferritin; and (vi) "case-mix plus laboratory plus UFR" adjusted model, which included covariates in the 'case-mix plus laboratory' adjusted model and UFR. The variance inflation factor metric showed that all covariates had variance inflation factor values below 2.0, indicating only moderate multicollinearity. After the primary analysis, we also conducted subgroup analyses for examining the association between a subgroup of low baseline renal CL_{urea} (<3.0 ml/min per 1.73 m^2) and cause-specific mortality stratified by age, sex, presence or absence of diabetes and cardiovascular disease, body mass index, UFR, serum albumin, highest potassium level and serum phosphorus including each interaction term into the case-mix adjusted model.

In the present study, we addressed lead-time bias by assessing changes in renal CL_{urea} using 2 measurements at appropriate intervals in addition to the baseline model. To address the lead-time bias in the association between baseline renal CL_{urea} and mortality, we then examined the association of changes in renal CL_{urea} during the first 6 months with each outcome. The changes in renal CL_{urea} were modeled as a continuous variable, and hazard ratios for each cause-specific mortality were estimated using restricted cubic spline functions with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of each index and referent at −1.5 ml/min per 1.73 m^2 of 6-month change. The first day of the third patient-quarter was used as the entry date. In the analyses of the association between 6-month change in renal CL_{urea} and cause-specific mortality, baseline variables were used to avoid overadjustment because these variables in the third patient-quarter may have been affected by changes in renal CL_{urea}. Adjustment for baseline renal CL_{urea} was added to all models evaluating the association of changes in renal CL_{urea} with mortality.

In sensitivity analyses, we assessed the association between 5 categories of baseline urine volume (<300, 300 to <600, 600 to <900, 900 to <1200, and ≥1200 ml/d) and cause-specific mortality using cause-specific proportional hazards models. We also examined the association of 6-month changes in urine volume with cause-specific mortality employing restricted cubic spline functions with 4 knots at the 5th, 35th, 65th, and 95th percentiles using the reference point of −300 ml/d.

All analyses were performed with Stata/MP 13.1 (Stata Corp., College Station, TX). Data were analyzed using the multiple imputation approach, applying chained equations methods to 5 datasets, assuming missing at random, and incorporated in all regression analyses. Missing baseline data were <1% for treatment parameters except for 5.9% of normalized protein catabolic rate, and <1% for laboratory measurements except for 3.8% of serum creatinine. A 2-tailed P-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Of the total 121,712 patients who initiated conventional hemodialysis from 2007 to 2011, excluding 126 patients with baseline renal CL_{urea} >15 ml/min per 1.73 m^2 and/or baseline urine volume >3000 ml/d, a total of 39,623 patients had baseline renal CL_{urea} values and were analyzed in the primary analyses (Figure 1). The mean age of the entire cohort was 61.6 (SD, 14.9) years, and the median urine volume was 800 (interquartile range, 500–1300) ml/d (Table 1). The median baseline renal CL_{urea} was 3.1 (interquartile range, 1.8–4.9) ml/min per 1.73 m^2, and the prevalence of baseline renal CL_{urea} categories <1.5, 1.5 to <3.0, 3.0 to <4.5, 4.5 to <6.0, and ≥6.0 ml/min per 1.73 m^2 were 19.6%, 27.7%, 22.2%, 14.0%, and 16.5%, respectively. There were statistically significant trends toward greater UFR and lower normalized protein catabolic rate across lower baseline renal CL_{urea}. In addition, the proportion of highest potassium levels increased with lower baseline renal CL_{urea}.

Baseline CL_{urea} and Cause-Specific Mortality

During a median observation period of 548 (interquartile range, 283–931) days, a total of 7723 patients died. Of those, "Missing" or "Unknown" was listed as a cause of death among 2753 deaths, and we observed 1905 SCDs, 867 non-SCD CVDs, and 2198 non-CVDs, which are summarized with incidence rate by each baseline renal CL_{urea} group shown in Table 2. Time-varying proportions of each cause of death by patient-quarter are shown in Supplementary Figure S1. Among documented causes of death excluding "Missing" and "Unknown" in Centers for Medicare and Medicaid Services form 2746, SCD ranged from 35.1% to 43.0%. There was a significant trend toward higher mortality risk across lower RKF irrespective of cause of death in the case-mix adjustment model (P_{trend} < 0.001 for SCD and non-CVD, and P_{trend} = 0.041 for non-SCD CVD; Figure 2). The mortality risk appeared to increase only with CL_{urea} <3.0 ml/min per 1.73 m^2 for SCD and <1.5 ml/min per 1.73 m^2 for non-SCD CVD. However, the association became more pronounced after laboratory adjustment for SCD and non-SCD CVD (Table 2). High risks of cause-specific mortality associated with the substantially low renal CL_{urea} categories (i.e., <3 ml/min per 1.73 m^2) appeared

Table 1. Baseline characteristics by categories of baseline renal urea clearance

	Baseline Renal Urea Clearance (ml/min per 1.73 m^2)					
	<1.5 (n = 7750 [19.6%])	1.5 to <3.0 (n = 10,991 [27.7%])	3.0 to <4.5 (n = 8783 [22.2%])	4.5 to <6.0 (n = 5544 [14.0%])	≥6.0 (n = 6555 [16.5%])	P_{trend}
Urine volume, ml/d	300 [200–450]	625 [500–900]	1000 [700–1350]	1250 [950–1650]	1550 [1150–2100]	<0.001
Age, yr	62.1 ± 15.9	61.8 ± 15.2	61.9 ± 14.6	61.3 ± 14.4	60.8 ± 14.1	<0.001
Male sex, n (%)	4152 (53.6%)	6483 (59.0%)	5664 (64.5%)	3829 (69.1%)	4838 (73.8%)	<0.001
Race, n (%)						
Non-Hispanic white	3885 (50.1%)	5820 (53.0%)	4961 (56.5%)	3382 (61.0%)	4002 (61.0%)	<0.001
Non-Hispanic black	2559 (33.0%)	3173 (28.9%)	2207 (25.1%)	1207 (21.8%)	1432 (21.9%)	<0.001
Hispanic	835 (10.8%)	1236 (11.2%)	979 (11.2%)	541 (9.7%)	639 (9.7%)	0.002
Other races	471 (6.1%)	762 (6.9%)	636 (7.2%)	414 (7.5%)	482 (7.4%)	0.7
Primary insurance, n (%)						
Medicare	4182 (54.0%)	5599 (51.0%)	4422 (50.4%)	2777 (50.1%)	3213 (49.0%)	<0.001
Medicaid	536 (6.9%)	739 (6.7%)	530 (6.0%)	294 (5.3%)	384 (5.9%)	<0.001
Others	3032 (39.1%)	4653 (42.3%)	3831 (43.6%)	2473 (44.6%)	2958 (45.1%)	<0.001
Comorbid conditions, n (%)						
Diabetes	4387 (56.6%)	6472 (58.9%)	5319 (60.6%)	3368 (60.8%)	4044 (61.7%)	<0.001
Hypertension	4157 (53.6%)	5791 (52.7%)	4465 (50.8%)	2730 (49.2%)	3048 (46.5%)	<0.001
Congestive heart failure	3207 (41.4%)	4359 (39.7%)	3383 (38.5%)	2118 (38.2%)	2380 (36.3%)	<0.001
Atherosclerotic heart disease	1103 (14.2%)	1616 (14.7%)	1296 (14.8%)	802 (14.5%)	1057 (16.1%)	0.003
Other cardiovascular disease	1299 (16.8%)	1724 (15.7%)	1364 (15.5%)	864 (15.6%)	1061 (16.2%)	0.5
Access type, n (%)						
AV fistula/graft	1098 (14.2%)	2219 (20.2%)	2225 (25.3%)	1450 (26.2%)	1465 (22.4%)	<0.001
Central venous catheter	6288 (81.1%)	8312 (75.6%)	6189 (70.5%)	3866 (69.7%)	4815 (73.4%)	<0.001
Unknown	364 (4.7%)	460 (4.2%)	369 (4.2%)	228 (4.1%)	275 (4.2%)	0.2
Treatment parameters						
Body mass index, kg/m^2	27.4 [23.4–33.3]	27.3 [23.6–32.6]	27.3 [23.6–32.4]	27.6 [23.9–32.7]	27.8 [24.0–32.8]	0.5
Weekday IDWG, %	2.3 [1.6–3.1]	2.2 [1.5–3.0]	2.1 [1.4–2.9]	2.0 [1.3–2.8]	2.0 [1.3–2.8]	<0.001
Weekend IDWG, %	3.2 [2.3–4.4]	3.0 [2.1–4.0]	2.8 [1.9–3.9]	2.6 [1.7–3.6]	2.5 [1.6–3.6]	<0.001
Ultrafiltration rate, ml/h/kg	7.8 ± 3.2	7.4 ± 3.1	7.1 ± 3.2	6.8 ± 3.2	6.7 ± 3.1	<0.001
single-pool Kt/V urea	1.38 ± 0.28	1.35 ± 0.28	1.31 ± 0.27	1.28 ± 0.27	1.25 ± 0.28	<0.001
nPCR, g/kg/d	0.86 ± 0.24	0.93 ± 0.25	1.00 ± 0.27	1.06 ± 0.28	1.13 ± 0.32	<0.001
Laboratory measurements						
Hemoglobin, g/dl	11.0 ± 1.1	11.2 ± 1.1	11.3 ± 1.0	11.4 ± 1.1	11.4 ± 1.1	<0.001
Albumin, g/dl	3.5 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	<0.001
Creatinine, mg/dl	6.9 ± 2.9	6.3 ± 2.4	5.7 ± 2.0	5.3 ± 1.8	4.5 ± 1.7	<0.001
Potassium, mEq/l	4.5 ± 0.5	4.5 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.3 ± 0.5	<0.001
Highest potassium level, n (%)						
K <5.0 mEq/l	4119 (53.2%)	6257 (56.9%)	5311 (60.5%)	3467 (62.5%)	4448 (67.8%)	<0.001
K 5.0 to <5.5 mEq/l	1879 (24.2%)	2588 (23.5%)	2069 (23.6%)	1265 (22.8%)	1362 (20.8%)	<0.001
K 5.5 to <6.0 mEq/l	1024 (13.2%)	1314 (12.0%)	925 (10.5%)	581 (10.5%)	529 (8.1%)	<0.001
K 6.0 to <6.5 mEq/l	472 (6.1%)	556 (5.1%)	336 (3.8%)	173 (3.1%)	156 (2.4%)	<0.001
K ≥6.5 mEq/l	253 (3.3%)	269 (2.5%)	142 (1.6%)	58 (1.0%)	60 (0.9%)	<0.001
Corrected calcium, mg/dl	9.1 ± 0.6	9.1 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	0.5
Phosphorus, mg/dl	5.2 ± 1.3	5.2 ± 1.1	5.0 ± 1.0	4.9 ± 1.0	4.5 ± 0.9	<0.001
Alkaline phosphatase, U/l	87 [68–116]	85 [67–110]	83 [66–107]	82 [66–106]	82 [66–107]	<0.001
Intact PTH, pg/ml	330 [206–520]	332 [214–509]	315 [206–474]	303 [197–448]	261 [168–392]	<0.001
Bicarbonate, mEq/l	23.8 ± 2.6	23.5 ± 2.6	23.3 ± 2.6	23.2 ± 2.6	23.3 ± 2.7	<0.001
Iron saturation, %	23 ± 9	23 ± 8	23 ± 8	23 ± 8	22 ± 8	0.001
TIBC, mg/dl	222 ± 47	229 ± 46	234 ± 46	239 ± 47	241 ± 49	<0.001
Ferritin, ng/ml	303 [177–509]	265 [157–441]	256 [150–429]	244 [144–407]	262 [151–441]	<0.001

AV, arteriovenous; IDWG, interdialytic weight gain; nPCR, normalized protein catabolic rate; TH, parathyroid hormone; TIBC, total iron-binding capacity.
Continuous variables are presented as mean ± standard deviation, or median (interquartile range). Categorical variables are presented as number (percent). Conversion factors for units: creatinine in mg/dl to μmol/l, ×88.4; corrected calcium in mg/dl to mmol/l, ×0.2495; phosphorus in mg/dl to mmol/l, ×0.3229.

to be attenuated by adjustment of UFR. In the sensitivity analysis, results remained consistent within the competing risk regression model (Supplementary Figure S2, Supplementary Table S2).

In subgroup analyses, compared with baseline renal CL_{urea} of ≥3.0 ml/min per 1.73 m^2, lower baseline renal CL_{urea} (<3.0 ml/min per 1.73 m^2) was associated with higher risk of SCD and noncardiovascular mortality overall and across all stratified groups after adjustment for case-mix covariates (Figure 3; Supplementary Table S3). Regarding noncardiovascular mortality, there were statistically significant interactions for body

Table 2. Associations between baseline renal urea clearance and cause-specific mortality in 39,623 incident hemodialysis patients

	Baseline Renal Urea Clearance (ml/min per 1.73 m^2)				
Cause-Specific Mortality	<1.5 (n = 7750 [19.5%])	1.5 to <3.0 (n = 10,991 [27.6%])	3.0 to <4.5 (n = 8,783 [22.2%])	4.5 to <6.0 (n = 5,544 [14.0%])	≥6.0 (n = 6,555 [16.5%])
Sudden Cardiac Death					
Events	445	542	393	254	271
Rates, per 1000 person-yrs	42.5	34.3	30.8	31.5	30.9
Cause-specific proportional hazards models					
Unadjusted	1.37 (1.18–1.60)	1.11 (0.96–1.28)	0.99 (0.85–1.16)	1.02 (0.86–1.21)	1.00 (reference)
Case-mix	1.45 (1.24–1.70)	1.15 (0.99–1.33)	1.02 (0.87–1.19)	1.03 (0.87–1.22)	1.00 (reference)
Case-mix + Highest K categories	1.45 (1.24–1.69)	1.15 (0.99–1.33)	1.01 (0.87–1.19)	1.03 (0.87–1.22)	1.00 (reference)
Case-mix + UFR	1.35 (1.16–1.58)	1.10 (0.95–1.28)	0.99 (0.85–1.17)	1.02 (0.86–1.21)	1.00 (reference)
Case-mix + Laboratory	1.74 (1.45–2.09)	1.33 (1.13–1.56)	1.13 (0.96–1.32)	1.10 (0.92–1.30)	1.00 (reference)
Case-mix + Laboratory + UFR	1.63 (1.35–1.96)	1.27 (1.08–1.50)	1.10 (0.93–1.30)	1.08 (0.91–1.29)	1.00 (reference)
Non-SCD cardiovascular death					
Events	197	229	185	123	133
Rates, per 1000 person-years	18.8	14.5	14.5	15.2	15.1
Cause-specific proportional hazards models					
Unadjusted	1.24 (0.99–1.54)	0.95 (0.77–1.18)	0.95 (0.76–1.19)	1.00 (0.79–1.28)	1.00 (reference)
Case-mix	1.38 (1.10–1.73)	1.01 (0.81–1.25)	0.97 (0.78–1.22)	1.01 (0.79–1.30)	1.00 (reference)
Case-mix + Highest K categories	1.37 (1.08–1.70)	1.00 (0.80–1.24)	0.97 (0.77–1.21)	1.01 (0.79–1.29)	1.00 (reference)
Case-mix + UFR	1.24 (0.99–1.56)	0.95 (0.76–1.18)	0.95 (0.76–1.18)	1.00 (0.79–1.28)	1.00 (reference)
Case-mix + Laboratory	1.76 (1.35–2.29)	1.23 (0.97–1.56)	1.13 (0.90–1.43)	1.11 (0.86–1.43)	1.00 (reference)
Case-mix + Laboratory + UFR	1.59 (1.22–2.08)	1.15 (0.90–1.46)	1.09 (0.86–1.38)	1.09 (0.85–1.40)	1.00 (reference)
Non-cardiovascular death					
Events	582	627	459	269	261
Rates, per 1000 person-years	55.6	39.7	35.9	33.3	29.7
Cause-specific proportional hazards models					
Unadjusted	1.87 (1.61–2.16)	1.33 (1.15–1.54)	1.21 (1.04–1.40)	1.12 (0.94–1.33)	1.00 (reference)
Case-mix	1.93 (1.66–2.24)	1.34 (1.16–1.55)	1.20 (1.03–1.39)	1.11 (0.93–1.31)	1.00 (reference)
Case-mix + Highest K categories	1.93 (1.66–2.24)	1.34 (1.16–1.55)	1.20 (1.03–1.39)	1.11 (0.93–1.31)	1.00 (reference)
Case-mix + UFR	1.83 (1.57–2.13)	1.30 (1.12–1.51)	1.18 (1.01–1.38)	1.10 (0.93–1.31)	1.00 (reference)
Case-mix + Laboratory	1.86 (1.56–2.21)	1.35 (1.15–1.58)	1.23 (1.05–1.45)	1.13 (0.95–1.35)	1.00 (reference)
Case-mix + Laboratory + UFR	1.79 (1.50–2.11)	1.31 (1.12–1.54)	1.22 (1.04–1.43)	1.12 (0.95–1.34)	1.00 (reference)

CI, confidence interval; K, potassium; SCD, sudden cardiac death; UFR, ultrafiltration rate.
Values in cause-specific proportional hazards models are given as hazard ratios (95% CI). Case-mix model adjusted for age, sex, race, primary insurance, access type, diabetes, hypertension, congestive heart disease, atherosclerotic heart disease, other cardiovascular disease, and single-pool Kt/V. Case-mix + laboratory model adjusted for covariates in the case-mix model, plus body mass index, normalized protein catabolic rate, hemoglobin, albumin, creatinine, highest potassium categories, phosphorus, alkaline phosphatase, iron saturation, bicarbonate, and ferritin.

mass index, highest potassium level, and phosphorus, with greater contributions of lower baseline renal CL_{urea} to higher mortality risk in patients with body mass index ≥28 kg/m^2, highest potassium level <5.0 mEq/l, and phosphorus <5.0 mg/dl ($P_{interaction} < 0.05$; Figure 3).

Association of Change in CL_{urea} With Cause-Specific Mortality

Among eligible 12,295 patients with available data on renal CL_{urea} both at first and third patient-quarter, excluding 126 patients with renal CL_{urea} >15 ml/min per 1.73 m^2, a total of 12,169 patients were identified. Of the 12,169 patients with data on 6-month change in renal CL_{urea} from baseline, 495 SCDs, 232 non-SCD CVDs, and 587 non-CVDs were observed during a median observation period of 743 (interquartile range, 496–1000) days. Restricted cubic spline functions showed graded associations of 6-month decline in renal CL_{urea} with increased SCD, non-SCD CVD, and non-cardiovascular mortality in case-mix adjusted models (Figure 4); case-mix adjusted hazard ratios were 1.14 (95% confidence interval, 1.03–1.27) in SCD, 1.24 (95% confidence interval, 1.08–1.43) in non-SCD CVD, and 1.19 (95% confidence interval, 1.07–1.32) in non-cardiovascular mortality at −3.0 ml/min per 1.73 m^2 of 6-month change in renal CL_{urea}, respectively, when compared to −1.5 ml/min per 1.73 m^2.

Urine Output as Another Measure of RKF

As a sensitivity analysis, baseline urine volume data were also available for the 39,623 patients (100%, Supplementary Table S4). There were consistent trends toward higher mortality risk across lower urine volume categories irrespective of cause of death ($P_{trend} < 0.001$ for all models; Figure 5, Supplementary Table S5). In addition, among 12,169 patients with available data on 6-month change in urine volume from baseline, there

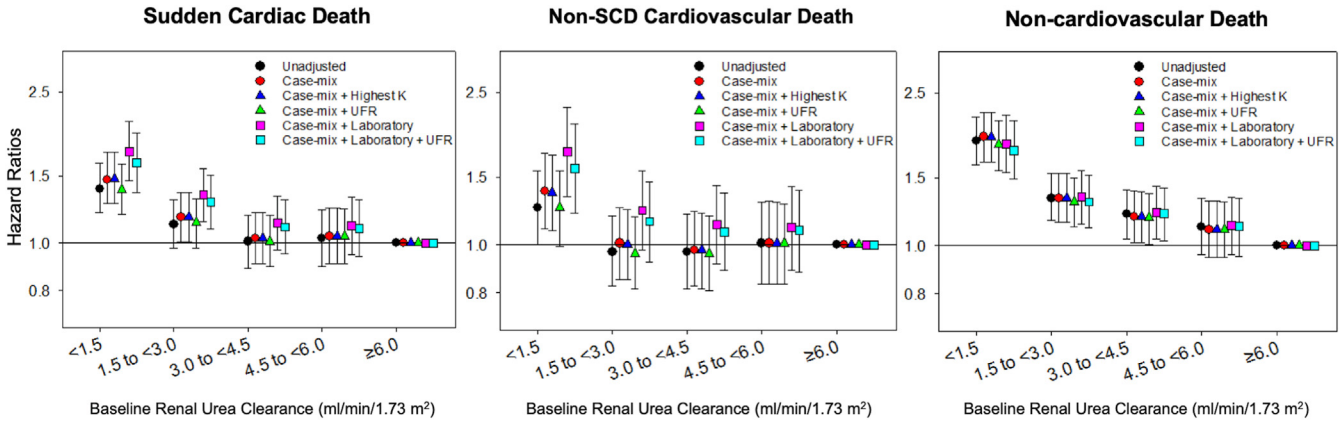

Figure 2. Multivariable-adjusted hazard ratios with 95% confidence intervals for cause-specific mortality in 39,623 incident hemodialysis patients. Hazard ratios were estimated by cause-specific proportional hazards models with 6-level adjustments using the renal CL_{urea} >6.0 ml/min per 1.73 m^2 as a reference group. Adjusted for "case-mix" model covariates: age, sex, race/ethnicity, primary insurance, comorbid conditions (hypertension, diabetes, congestive heart failure, atherosclerotic heart disease, other cardiovascular disease), vascular access type, and single-pool Kt/V. Adjusted for "case-mix plus laboratory plus UFR" model covariates: case-mix model covariates plus body mass index, nPCR, hemoglobin, serum albumin, creatinine, highest potassium categories, phosphorus, iron saturation, bicarbonate, alkaline phosphatase, ferritin, and ultrafiltration rate at baseline of the first 91-day period. CL_{urea}, urea clearance; highest K, highest potassium categories; nPCR, normalized protein catabolic rate; SCD, sudden cardiac death; UFR, ultrafiltration rate.

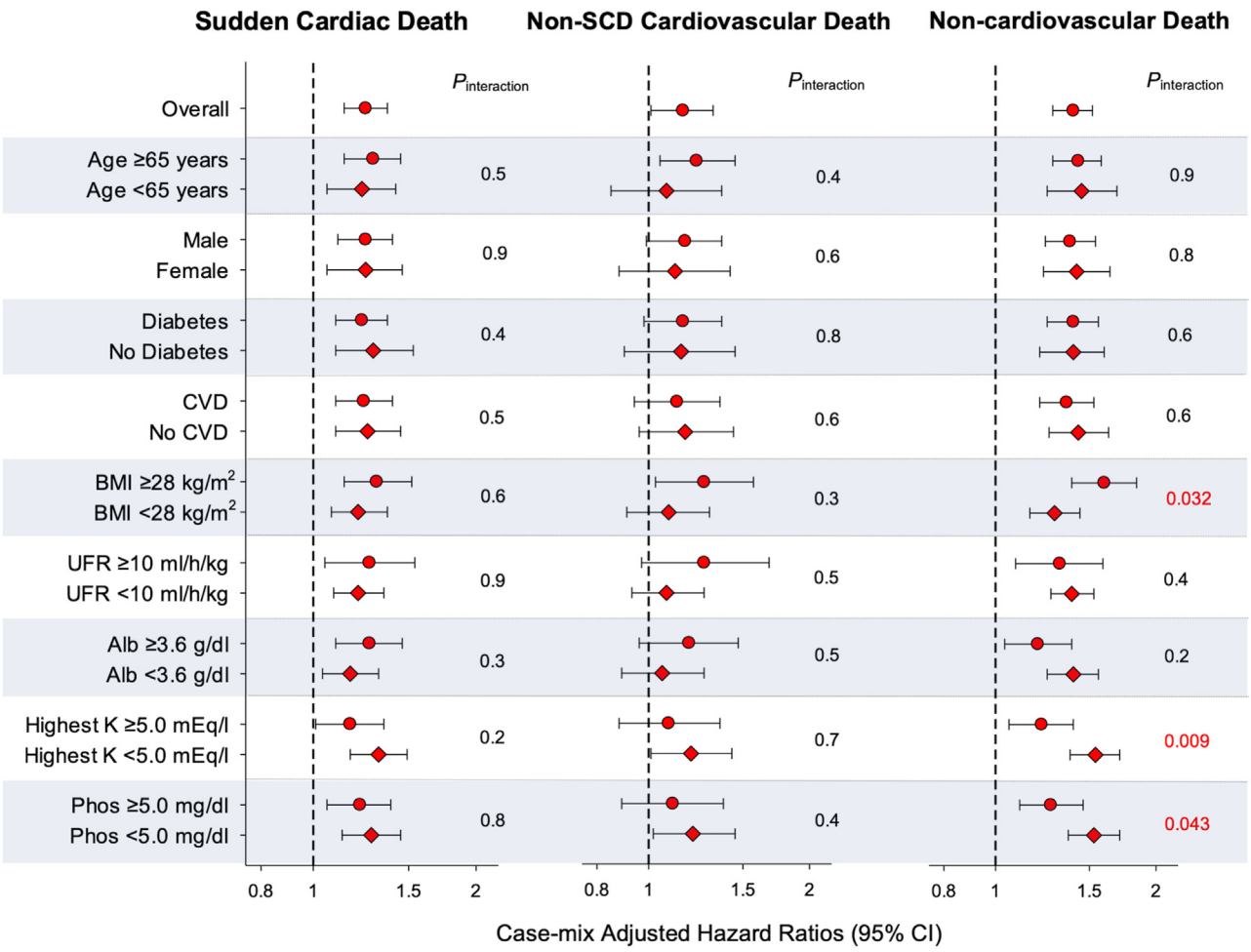

Figure 3. Subgroup analyses of the associations between lower baseline renal CL_{urea} <3 ml/min per 1.73 m^2 and cause-specific mortality in 39,623 incident hemodialysis patients. Adjusted hazard ratios with 95% confidence intervals were estimated by case-mix adjustment model including age, sex, race/ethnicity, primary insurance, comorbid conditions (hypertension, diabetes, congestive heart failure, atherosclerotic heart disease, other cardiovascular disease), vascular access type, and single-pool Kt/V. Alb, serum albumin; BMI, body mass index; CL_{urea}, urea clearance; CVD, cardiovascular disease; Highest K, highest potassium level; Phos, serum phosphorus; SCD, sudden cardiac death; UFR, ultrafiltration rate.

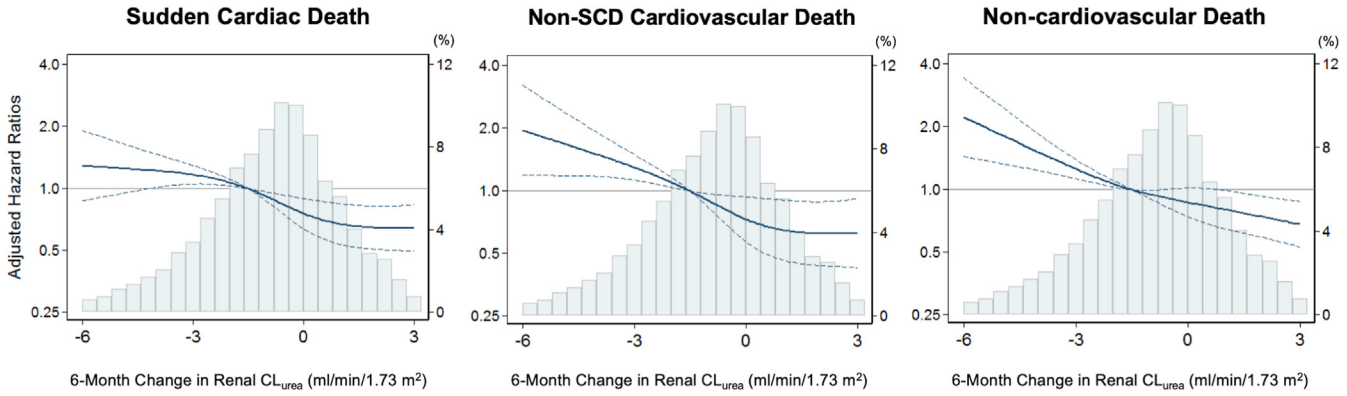

Figure 4. Association between 6-month change in renal CL_{urea} and cause-specific mortality among 12,169 incident hemodialysis patients. The change in renal CL_{urea} is modeled as restricted cubic splines with 4 knots and centered at −1.5 ml/min per 1.73 m^2 (reference point) Changes in renal CL_{urea} were calculated subtracting values at the third patient-quarter from those at baseline. Model is adjusted for age, sex, race/ethnicity, primary insurance, comorbid conditions (hypertension, diabetes, congestive heart failure, atherosclerotic heart disease, other cardiovascular disease), vascular access type, single-pool Kt/V, and baseline values of renal CL_{urea}. Solid lines indicate point estimates of hazard ratio and corresponding 95% confidence intervals are shown in dashed lines. Histograms represent the distribution of changes in renal CL_{urea} over the first 6 months period. CL_{urea}, urea clearance; SCD, sudden cardiac death.

were graded associations of faster 6-month decline in urine volume with higher SCD and noncardiovascular mortality, although the graded association with non-SCD CVD mortality was not evident (Figure 6).

DISCUSSION

In this large national cohort of 39,623 patients starting thrice-weekly in-center hemodialysis in the United States, lower baseline renal CL_{urea} was consistently associated with greater mortality across 3 categories of causes of death, that is, SCD, non-SCD CVD, and non-CVD. These robust associations with SCD and non-CVD were consistent across strata of demographics and relevant clinical factors. In addition, a decline in renal CL_{urea} during the first 6 months of hemodialysis also showed a graded association with increased mortality in SCD, non-SCD CVD, and non-CVD.

Several cohort studies have demonstrated that loss of RKF is associated with higher all-cause mortality among patients undergoing hemodialysis as well as those on peritoneal dialysis.[3,4,30] Our prior studies also reported that annual declines in RKF, as measured by both renal CL_{urea} and urine output, were significantly associated with increased all-cause mortality in incident hemodialysis patients.[5,23] In the present study, we extended these prior observations by investigating its association with each cause of death.

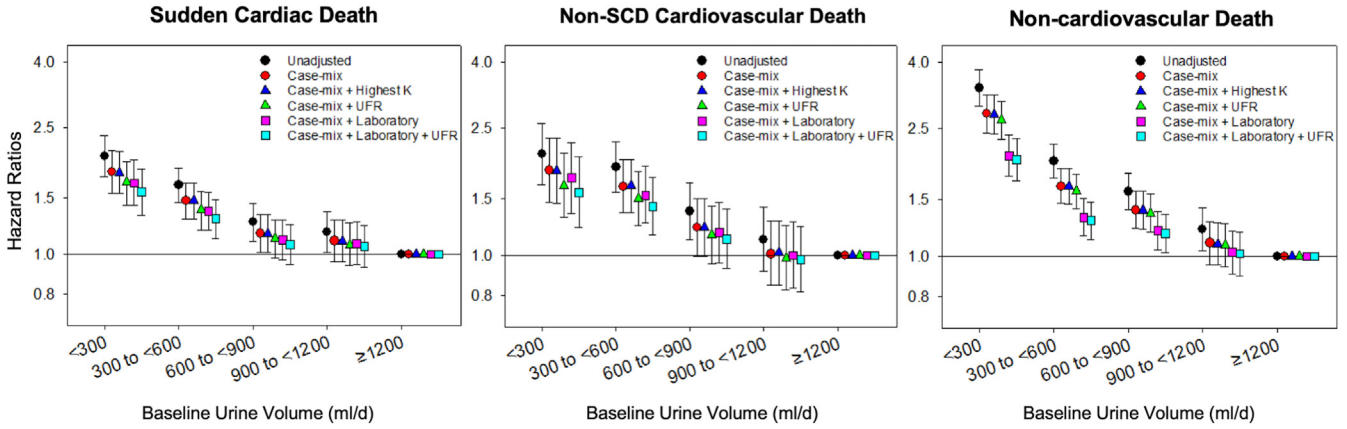

Figure 5. Graded association of lower baseline urine volume with higher cause-specific mortality in 39,623 incident hemodialysis patients. Hazard ratios were estimated by cause-specific proportional hazards models with 6-level adjustments using the baseline urine volume >1200 ml/d as a reference group. Adjusted for "case-mix" model covariates: age, sex, race/ethnicity, primary insurance, comorbid conditions (hypertension, diabetes, congestive heart failure, atherosclerotic heart disease, other cardiovascular disease), vascular access type, and single-pool Kt/V. Adjusted for "case-mix plus laboratory plus UFR" model covariates: case-mix model covariates plus body mass index, nPCR, hemoglobin, serum albumin, creatinine, highest potassium categories, phosphorus, iron saturation, bicarbonate, alkaline phosphatase, ferritin, and ultrafiltration rate at baseline of the first 91-day period. highest K, highest potassium categories; nPCR, normalized protein catabolic rate; SCD, sudden cardiac death; UFR, ultrafiltration rate.

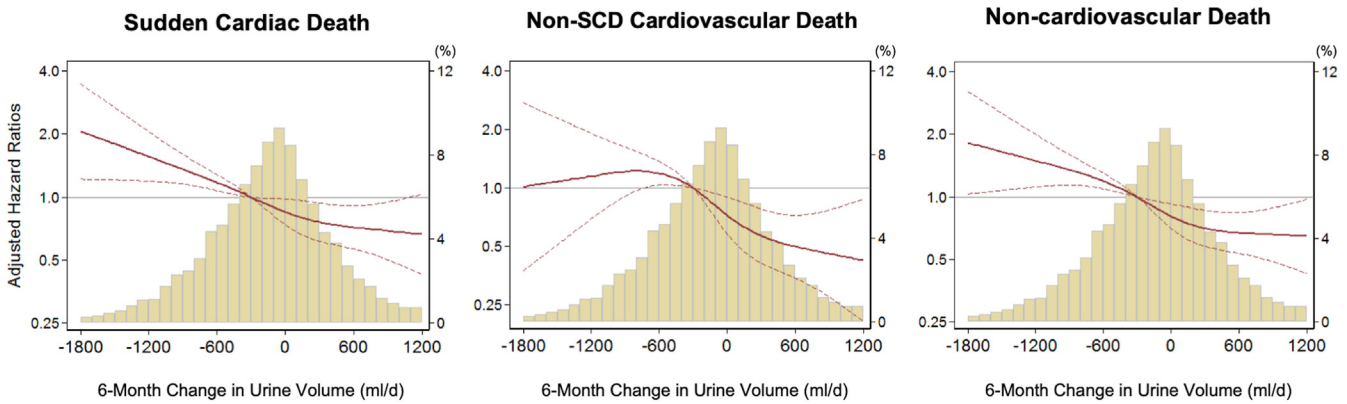

Figure 6. Association between 6-month change in urine volume and cause-specific mortality in 12,169 incident hemodialysis patients. The change in urine volume is modeled as restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles using the reference point of −300 ml/d. The model is adjusted for age, sex, race/ethnicity, primary insurance, comorbid conditions (hypertension, diabetes, congestive heart failure, atherosclerotic heart disease, other cardiovascular disease), vascular access type, single-pool Kt/V, and baseline urine volume. Histograms represent the distribution of changes in urine volume 6 months after initiation of maintenance hemodialysis. SCD, sudden cardiac death.

In our study, we observed significant associations between low residual renal CL_{urea} and higher risk of noncardiovascular mortality, as well as presumed associations with cardiovascular mortality. Notably, the observed relationship between lower levels of renal CL_{urea} and noncardiovascular mortality appeared to be stronger than those between baseline renal CL_{urea} and non-SCD CVD mortality. There are several potential mechanisms by which substantial RKF may relate to improved noncardiovascular mortality. Preserved RKF may contribute to the prevention or treatment of protein-energy wasting through the alleviation of dietary restrictions leading to greater dietary protein intake.[4,6] Protein-energy wasting results from multiple mechanisms, including hypercatabolic status, malnutrition, uremic toxin retention, and inflammation, and may lead to infection and frailty as well as cardiovascular disease.[31,32] In fact, our subgroup analyses also suggested the contribution of lower baseline renal CL_{urea} to higher noncardiovascular mortality was more apparent in a subgroup with baseline serum albumin <3.6 mg/dl compared to SCD mortality. In addition, we found that greater urine output was associated with lower noncardiovascular mortality, which may be attributed to nutritional advantages including liberalized dietary intake. Therefore, the associations between lower RKF and higher risk of noncardiovascular mortality may be related to the complex effects of protein-energy wasting. Second, substantial RKF may lead to enhanced removal of protein-bound solutes, as well as middle molecule clearance.[8,33] For example, levels of p-cresol sulfate, a well-studied protein-bound solute which has a negative impact on the cardiovascular system, tend to be lower in patients with preserved RKF than in patients without RKF.[7] Several biologic studies have indicated that protein-bound uremic toxins have adverse multifaceted effects, including endothelial dysfunction,[34,35] leukocyte activation,[36] and immune response disfunction,[15,16,18,37] and may contribute to infections, the leading cause of non-CVD in patients on hemodialysis. Although there are many risk factors with common mechanisms in cardiovascular and noncardiovascular mortality, our results may highlight the possible influence of uremic retention solutes especially on noncardiovascular mortality among patients starting hemodialysis.

Despite the abundant prior literature, the optimal timing of dialysis initiation remains unclear. In fact, the randomized controlled trial of Initiating Dialysis Early and Late study did not demonstrate any clinical benefit in starting dialysis at higher estimated glomerular filtration rate levels.[38] In addition, a recent Swedish nationwide observational study rigorously tried to eliminate lead-time/immortal bias by target trial emulation design and found only a modest reduction in mortality and cardiovascular events associated with very early dialysis initiation.[39] Our present study addressed lead-time bias employing the longitudinal changes in RKF. Our findings do not explicitly advocate for early initiation of dialysis, but rather suggest that strategies to preserve RKF might be considered in future clinical trials of incident hemodialysis patients.

We acknowledge several other limitations to consider. First, RKF measured by urinary clearance has inherent difficulties associated with urine collection in daily practice, including errors in collection and incomplete bladder emptying. In addition, the method of calculating renal CL_{urea} using factor 0.9 for predialysis serum urea nitrogen[22] may relate to inaccuracy compared to true glomerular filtration rate. However,

renal CL_{urea} generally underestimates the true glomerular filtration rate, and therefore our results would provide conservative estimates of the contribution of RKF to cause-specific mortality. Second, it should be noted that the patients with little or no urine output were less likely to have timed urine collection after starting hemodialysis. This potential selection bias may have resulted in missing patients who lost RKF 6 months after initiating hemodialysis, resulting in an underestimation of the risk of mortality, especially of an early onset nature such as SCD. Third, due to the nature of this nationwide epidemiological study, it is plausible that the true cause of death for many patients categorized as "Missing" or "Unknown" may contain cardiovascular disease, including SCD.[25,40] Two previous studies that rigorously adjudicated SCD suggested that the sensitivity and specificity was 70.8% and 90.7%, respectively, for simple SCD defined as "cardiac arrhythmia" or "cardiac arrest, cause unknown" in the Centers for Medicare and Medicaid Services form 2746.[12,25] Therefore, our simple definition of SCD that was based on the Centers for Medicare and Medicaid Services form 2746 may have some misclassification. Fourth, in subgroup analyses reporting the interactions between several strata with the lower renal CL_{urea} and noncardiovascular mortality, some of the significant interactions observed may have been chance findings as a consequence of multiple testing. Lastly, as with all observational studies, we cannot eliminate the residual confounding (e.g., availability of health care resources, reasons for dialysis initiation, and severity of comorbidities) that might have affected the associations evaluated in this study.

In conclusion, in a large observational cohort study, lower RKF and loss of RKF were associated with higher cause-specific mortality among incident hemodialysis patients. Future clinical trials are warranted to demonstrate the benefits of interventions to preserve RKF, such as an incremental hemodialysis and/or emerging renoprotective pharmacotherapies, and whether these interventions improve high mortality in patients undergoing hemodialysis.

DISCLOSURE

KKZ has received honoraria and/or support from Abbott, AbbVie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO Oncology, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations, International Society of Hemodialysis, International Society of Renal Nutrition & Metabolism, Japanese Society of Dialysis Therapy, Hospira, Kabi, Keryx, Novartis, National Institutes of Health, National Kidney Foundation, OPKO, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZSPharma. YO has received honoraria and/or support from Vifor/Relypsa. The remaining authors declare no relevant conflicting interests.

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DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are not publicly available due to containing information that could compromise the privacy of research participants. The corresponding author will detail the restrictions and conditions under which access to some data may be provided upon reasonable request.

AUTHOR CONTRIBUTIONS

Research idea and study design was by MO, YO, TS, and KKZ; data acquisition was by MO; data analysis/interpretation were by MO, YO, TS, CMR, CPK and KKZ; statistical analysis was by MO, YO, and TS; supervision or mentorship was by YO, TS, and KKZ. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the author's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Method S1. Calculation of normalized protein catabolic rate incorporating renal urea clearance.

Figure S1. Time varying cause-specific mortality in 39,623 incident hemodialysis patients.

Figure S2. Multivariable-adjusted subdistribution hazard ratios with 95% confidence intervals for cause-specific mortality in 39,623 incident hemodialysis patients.

Table S1. Definitions of each cause of death based on the specific codes utilized in the Centers for Medicare and Medicaid Services Death Notification form 2746.

Table S2. Subdistribution hazard ratios for cause-specific mortality across categories of baseline renal urea clearance in 39,623 incident hemodialysis patients.

Table S3. Case-mix adjusted hazard ratios and 95% confidence intervals for cause-specific mortality with lower baseline renal CL_{urea} <3 ml/min/1.73 m^2 (vs. baseline renal CL_{urea} ≥ 3.0 ml/min/1.73 m^2) in clinically relevant subgroups among 39,623 incident hemodialysis patients.

Table S4. Patient characteristics stratified by baseline urine volume.

Table S5. Associations between baseline urine volume and cause-specific mortality among 39,623 incident hemodialysis patients.

STROBE Statement.

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